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Qsar Study of Rabbit Aortic Angiotensin II Antagonists Compounds Using Different Descriptors

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ABSTRACT

For present study, the various QSAR models have been developed to predict the activities in terms of log 1/C for 11 Rabbit Aorta Angiotensin II Antagonists compounds with the help of quantum chemical and energy descriptors viz. heat of formation, Gibbs free energy, Molar Refractivity, HOMO energy, LUMO energy, absolute hardness, Softness, Chemical Potential and electronegativity. The parameter adopted in this calculation is the semi-empirical PM3 based. The QSAR model sixth provides a good arrangement between obs log 1/c & predicted activity.

Keywords: PM3, Absolute Hardness, Global Softness; electronegativity, Chemical potential, hardness, HOMO, LUMO, Heat of formation(ΔH), Gibbs free energy (ΔS), Molar Refractivity (MR).

1. INTRODUCTION

The use of quantitative structure-activity relationships (QSAR) since their advent in[1] has become increasingly helpful in understanding many aspects of chemical-biological interactions in drug and pesticide research as well as many areas of toxicology. With a properly designed set of congeners, carefully tested in almost any biological system, it has become easy to derive a QSAR by a steadily increasing number of computerized approaches. Getting a new QSAR no longer calls for rushing into print. What is called for is support for it from as many points of view as possible. In fact, there are so many fancy new programs that almost any set of chemicals acting on a given system can be correlated mathematically. Some wit has remarked that if you cannot derive a correlation equation it is a bad reflection on your library since there seems to be an almost unlimited selection of parameters.

The real problem is to deduce when the result can be related to our general knowledge of chemistry and biology. For work in progress, one can test new molecules to check the equation, but for most published work, this is not possible. We are finding that lateral support is possible in a variety of ways[2-10]. From the beginning to present day, luck has played a major role in drug discovery.[11] In the present report, we review nonpeptide angiotensin antagonists. The vasoactive hormone angiotensin II produced by the renin-angiotensin system (RAS) plays an integral role in the pathophysiology of hypertension because it effects the regulation of fluid volume, electrolyte balance, and blood volume in mammals.[12-13] Renin is a proteolytic enzyme produced mainly in the juxtaglomerular apparatus of the kidney, which acts on the circulating α-globulin angiotensinogen produced by the liver.[14]

In the present study we have taken structures of a set of compounds Angiotensin II and then compared to the numerical values of a biological activity. The goal here has been to find some numerical information for a molecule. This structure information and the measured property or activities are then converted into a mathematical model of relationship. From a quality model it is possible to predict and to design compounds for synthesis and testing that have a good possibility for activity. In this paper, the multi linear regression analysis has been applied for QSAR study. The relationship has been worked out between the Log1/C values of a series of compounds and certain quantum chemical descriptors.

2. THE STUDY MATERIAL

The compounds taken for study are Rabbit Aortic derivatives of Angiotensin II and shown in Fig.-1.

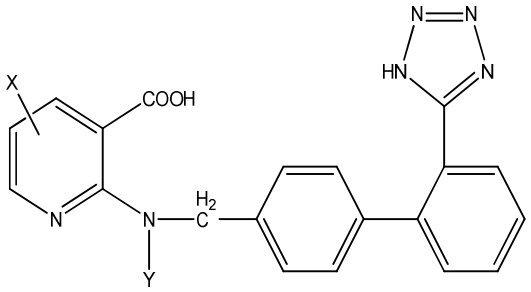

Fig.-1:

3. METHODOLOGY

The Quantum Mechanical QSAR

The Quantum Chemical parameter based QSAR study was performed by the following important descriptors like Chemical Potential (μ)[16], Absolute Hardness(□)[19], Global Softness (S)[18], Electronegativity (χ)[19], Eigen value of Highest occupied molecular orbital (EHOMO), Eigen value of lowest unoccupied molecular orbital (ELUMO), Heat of formation(ΔH), Gibbs free energy (ΔS), Molar Refractivity (MR). The molecules were drawn by spartan06v110, software and the geometries were optimized at PM3 level in conjunction with molecular mechanics. The global hardness and electronegativities were calculated using frontier orbital energies obtained from PM3 results and reported in Tables 2. Multiple linear regression analysis (MLR) is performed to establish the QSAR.

A data set of Rabbit Aortic of Angiotensin II compounds were taken with their observed activity is shown in table 1.

Table 1

Comp.No.	X	Y	Obsd log 1/C
1	H	C_3H_7	10.100
2	4-CH_3	C_3H_7	9.640
3	5-CH_3	C_3H_7	8.800
4	5-Cl	C_3H_7	9.070
5	5-F	C_3H_7	9.040
6	5-I	C_3H_7	8.380
7	5-C_6H_5	C_3H_7	8.910
8	5-NO_2	C_3H_7	8.330
9	5-NH_2	C_3H_7	7.600
10	$NHCOCH_3$	C_3H_7	7.900
11	CH_3	C_3H_7	8.150

Table 2 Calculated numeric values of Rabbit Aortic derivatives of Angiotensin II by using different descriptors.

E LUMO (e.v)	E HOMO (e.v)	η	S	χ	MR (cm3/mol)	ΔH (kJ/mol)	ΔG (kJ/mol)
-0.914	-9.180	4.133	8.087	5.047	131.600	227.810	782.850
-1.024	-9.351	4.163	8.375	5.188	130.310	232.710	762.500
-0.965	-9.188	4.111	8.151	5.076	126.110	52.340	579.620
-0.944	-9.106	4.081	8.047	5.025	142.800	304.680	840.970
-1.007	-8.989	3.991	7.996	4.998	155.900	340.500	654.500
-1.007	-8.989	3.991	7.996	4.998	132.600	224.500	945.780
-0.828	-9.065	4.118	7.857	4.947	135.130	261.600	849.300
-0.995	-9.145	4.075	8.140	5.070	143.470	74.320	740.610
-0.890	-9.185	4.148	8.061	5.037	130.640	227.810	782.850
-1.001	-9.390	4.195	8.391	5.195	126.840	252.340	579.620
-0.908	-8.732	3.912	7.630	4.820	132.840	95.590	677.850

Multiple linear regression (MLR) analysis

MLR analyses were performed using Minitab 16 software. The quantum mechanical descriptors were used as independent variables and the obsd log1/C50 values as the dependent variables. In the statistical analyses, the systematic search was performed to determine the significant descriptors. The correlation matrix was developed to minimize the effect of co-linearity and to avoid redundancy and the variables physically removed from the analysis, which shows exact linear

dependencies between subsets of the variables and multi-co-linearity (high multiple correlations between subsets of the variables). The MLR equations of different QSAR models are as fallows-

First QSAR model

MLR equation of this QSAR model log 1/C is given by-
Obsd log 1/C = 2.41 - 6.40 E LUMO
S = 0.520140
PRESS = 3.33043
r^2= 39.2%

Second QSAR model

MLR equation of this QSAR model log 1/C is given by-
Obsd log 1/C = - 12.3 - 4.76 E LUMO - 1.79 E HOMO
S = 0.431588
PRESS = 2.53884
r^2= 62.8%

Third QSAR model

MLR equation of this QSAR model log 1/C is given by-
Obsd log 1/C = 43.0 + 25.6 E LUMO + 24.2 E HOMO + 26.1 S
S = 0.439751
PRESS = 2.45686
r^2= 38.65%

Fourth QSAR model

MLR equation of this QSAR model log 1/C is given by-
Obsd log 1/C = 39.9 + 22.4 E LUMO + 21.9 E HOMO + 23.7 S - 0.0070 MR
S = 0.470021
PRESS = 4.97156
r^2= 66.9%

Fifth QSAR model

MLR equation of this QSAR model log 1/C is given by-
Obsd log 1/C = 68.3 + 33.9 E LUMO + 33.1 E HOMO + 34.3 S - 0.0223 MR + 0.00252 ΔH

S = 0.439634
PRESS = 8.14412
r^2= 75.9%

Sixth QSAR model

MLR equation of this QSAR model log 1/C is given by-
Obsd log 1/C = 48.1 + 19.2 E LUMO + 20.5 E HOMO + 21.1 S - 0.0287 MR + 0.00377 ΔH - 0.00267 ΔG
S = 0.257392
PRESS = 3.44928
r^2= 93.4%

Sixth QSAR model

MLR equation of this QSAR model log 1/C is given by-
Obsd log 1/C = 48.1 + 19.2 E LUMO + 20.5 E HOMO + 21.1 ΔS - 0.0287 MR + 0.00377 H - 0.00267 ΔG
S = 0.257392
PRESS = 3.44928
r^2= 93.4%

This is one of the best QSAR model in all the six models and has been developed using E LUMO, ELUMO, Global Softness (S), Molar Refractivity (MR), Heat of reaction (ΔH) and Gibbs free energy

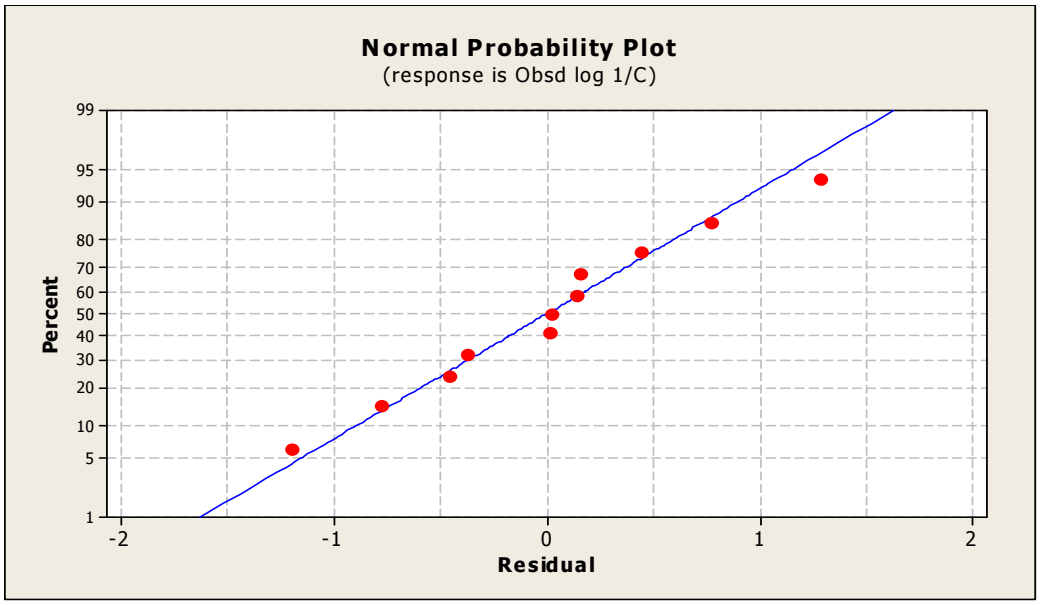

Fig: - 1 Normal probability plot of responses of QSAR model Sixth

4. CONCLUSION

Values of the descriptors of the Angiotensin II Antagonist derivatives have been calculated using PM3 method and are given in Table-2. With the help of these values of descriptors, six QSAR models have been developed using MLR analysis in different combinations of descriptors. The Chemical Potential (μ) and Absolute Hardness (□) descriptors have no predicting power and hence not included in the models. Best QSAR models is the model sixth listed below-

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